Minireview

Protein translocation pathways of the mitochondrion

Carla M. Koehler*

Department of Chemistry and Biochemistry, Box 951569, University of California, Los Angeles, CA 90095-1569, USA

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Abstract The biogenesis of mitochondria depends on the coordinated import of precursor proteins from the cytosol coupled with the export of mitochondrially coded proteins from the matrix to the inner membrane. The mitochondria contain an elaborate network of protein translocases in the outer and inner membrane along with a battery of chaperones and processing enzymes in the matrix and intermembrane space to mediate protein translocation. A mitochondrial protein, often with an amino-terminal targeting sequence, is escorted through the cytosol by chaperones to the TOM complex (translocase of the outer membrane). After crossing the outer membrane, the import pathway diverges; however, one of two TIM complexes (translocase of inner membrane) is generally utilized. This review is focused on the later stages of protein import after the outer membrane has been crossed. An accompanying paper by Lithgow reviews the early stages of protein translocation.

Key words: Mitochondrion; Protein targeting; Membrane; Protein translocation; Translocase

1. Introduction

The mitochondrion is a structurally complex organelle in the eukaryotic cell, containing an outer and inner membrane, which separate the matrix from the intermembrane space. This organelle contains its own small genome that encodes a handful of inner membrane proteins of the mitochondrial energy producing system. As in bacteria, these proteins are exported from the matrix to the inner membrane, although the export components generally are quite different between bacteria and the mitochondrial inner membrane [1]. Even though mitochondrial protein import has been studied intensively for the past two decades, new protein translocation systems have recently been identified in the mitochondrial inner membrane that mediate the import (and export) of inner membrane proteins (Fig. 1).

Most mitochondrial precursors contain an amino-terminal targeting presequence, but many proteins, particularly those of the outer and inner membrane, contain targeting and sorting information within the mature part of the protein. Based on studies focused on the import and sorting of model mitochondrial proteins or synthetic fusion proteins between a mitochondrial targeting sequence and a passenger protein, a translocation system is present in both the outer and inner membrane (reviewed by [2–6]). The translocase of the outer membrane (TOM) consists of protein import receptors and the import channel. The receptors (Tom20, 22, 37 and 70, with the number indicating molecular weight) on the mitochondrial surface recognize targeting information on mitochondrial precursors, while components Tom40 and the small Tom proteins 5, 6 and 7 form the channel through which the translocating precursor passes [6]. After passage through the TOM complex, proteins are sorted via a number of mechanisms either directly to the outer membrane, the intermembrane space, or the translocase of the inner membrane (TIM). Generally, the TIM23 machinery mediates protein translocation into the matrix and the TIM22 machinery mediates insertion into the inner membrane.

2. The TIM23 complex is the translocase of the general import pathway

Precursors with an amino-terminal targeting presequence follow the general import pathway (Fig. 2; [7–9]); their import is mediated by the Tim17/Tim23 complex (designated TIM23) and the translocation motor consisting of Tim44, mitochondrial heat shock protein hsp70 and the nucleotide exchange factor mGrpE. This translocation is dependent upon the presence of a membrane potential ($\Delta\psi$) and gener-

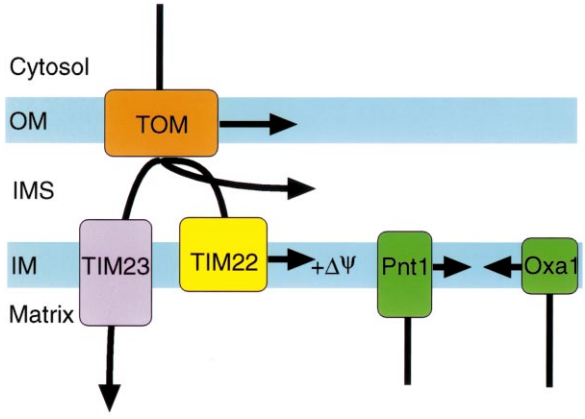

Fig. 1. Protein import and export pathways in the mitochondrion. Cytosolic proteins are imported through the TOM and then, depending upon their destination, remain in the outer membrane (OM), intermembrane space (IMS), or engage the translocases of the inner membrane (TIM). Precursors with a typical amino-terminal targeting sequence generally engage the TIM23 complex, whereas proteins that reside in the inner membrane (IM), often lacking a targeting sequence, engage the TIM22 complex. Mitochondrial encoded proteins may be exported to the inner membrane via Oxa1 and Pnt1. Pathways are depicted schematically by arrows. See text for details.

*Fax: (1)-310-206 4038.
E-mail: koehlerc@chem.ucla.edu

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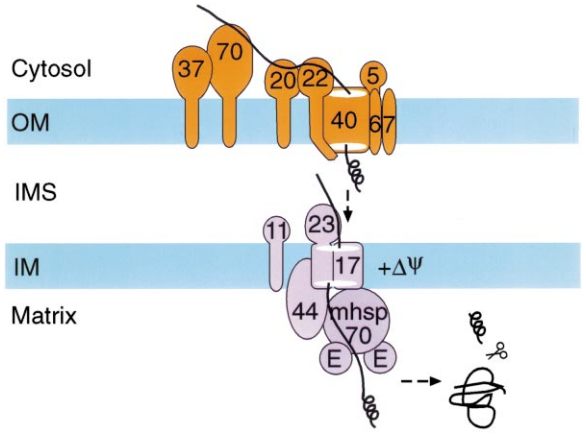

Fig. 2. Import of proteins across the inner membrane into the matrix. This pathway is mediated by the Tim17/Tim23 complex and an associated ATP-driven protein transport motor on the inner face of the inner membrane. As a precursor with an amino-terminal basic matrix-targeting signal (helical line) emerges from the TOM complex, it binds to an acidic Tim23 domain in the intermembrane space and thereby induces transient docking of the TOM and the Tim17/Tim23 system. A consequence of docking is that the precursor is not released into the intermembrane space. In the matrix, the matrix processing protease (scissors) removes the matrix-targeting sequence and a battery of chaperones may aid in folding to generate the mature protein. See text for further details. OM, IMS, IM: outer membrane, intermembrane space, inner membrane, respectively.

ally requires ATP hydrolysis by mhsp70 on the matrix side for unidirectional translocation. The TIM23 complex acts independently of the TOM complex although the two can be reversibly associated while a precursor is in transit [10,11]. All components of this translocase are essential for viability in *Saccharomyces cerevisiae*.

The Tim channel of the inner membrane is comprised of two related proteins, Tim17 and Tim23 [12–15]. Both proteins have four putative membrane spanning domains, and Tim23 contains a negatively charged domain in the intermembrane space that recognizes precursors taking the general import route. Tim17 and Tim23 are partner proteins in a 90 kDa complex in the inner membrane. Tim23 has been proposed to form a dimer in the absence of a membrane potential such that the import channel is closed [16]; binding of the intermembrane space domain to Tim23 then triggers dimer dissociation, allowing the precursor to pass through the import channel.

The matrix-sided components, Tim44, mhsp70 and mGrpE, function as the ATP-dependent translocation motor [17–21]. Tim44 is stably associated with the inner membrane but is mainly exposed at the matrix side. After the initial $\Delta\psi$-driven translocation of the N-terminal targeting sequence, mhsp70 is required for the translocation of the remainder of the precursor across the inner membrane [22–24]. The co-chaperone mGrpE is a matrix protein homologous to the nucleotide exchange factor GrpE of bacteria [19,21]. mGrpE interacts with mhsp70 bound to a precursor and promotes the reaction cycle of mhsp70, thereby allowing nucleotide release [25,26]. Three models, still under much debate, have been proposed to explain the role of mhsp70 in protein import: (1) the Brownian rachet which proposes mhsp70 traps the precursor [27,28], (2) an import motor in which hsp70 actively pulls the precursor [29], and (3) a model in which mhsp70 both pulls and traps [30,31].

To date, additional proteins in this TIM machinery have been identified, but their specific role in protein import has not been determined. Tim11 was identified because of its intimate association with the Tim channel [32]. Studies with a cytochrome b_2 arrested translocation intermediate and a cross-linker with a short spacer arm cross-linked Tim11 with very high specificity. Further studies revealed it is also the γ-subunit of the mitochondrial ATPase and is an ATPase assembly factor [33]. Studies by Endo and colleagues, based on the presence of site-specific cross-links with a mitochondrial precursor with a classical targeting sequence, have revealed other proteins that also might play a role in import [34]. Of these, a 50 kDa protein is identified as a potential new import component [34].

3. TIM22 protein import pathway mediates insertion of inner membrane proteins

Many inner membrane proteins lack a cleavable targeting sequence, carrying instead their targeting and sorting information within the 'mature' part of the polypeptide chain. This category of proteins includes at least 34 members of the yeast mitochondrial carrier family [35], which span the inner membrane six times, as well as the TIM components. The mechanism by which these inner membrane proteins cross the hydrophilic intermembrane space and then insert correctly into the inner membrane has been uncertain until recently; a new protein import pathway (designated TIM22) that acts specifically on inner membrane proteins has been identified (Fig. 3) [36–41]. Components in this pathway are located in the mitochondrial inner membrane and intermembrane space.

3.1. Inner membrane components of TIM22 import pathway

Tim22, an essential inner membrane protein, was the first component identified based on homology to Tim17 and

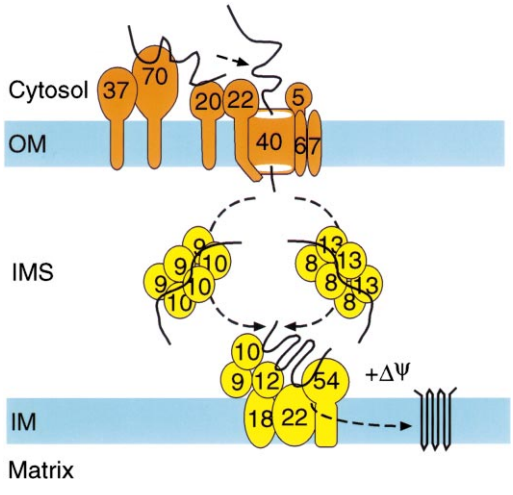

Fig. 3. Import of proteins into the mitochondrial inner membrane. As the precursor emerges from the TOM complex, it binds to the Tim9/Tim10 or Tim8/Tim13 complex of the intermembrane space. The bound precursor is then usually delivered to an insertion complex composed of Tim10, Tim12, Tim18, Tim22 and Tim54 that catalyzes the membrane potential ($\Delta\psi$)-dependent insertion of the precursor into the inner membrane [48]. An alternative model (not shown here) proposes that the Tim9/Tim10 complex receives the precursor directly from the TOM complex and passes it to the Tim22/Tim54 complex through formation of a translocation contact site [40,49]. See text for details.

Tim23 [42]. Surprisingly, depletion of Tim22 did not affect the general import pathway but inhibited the insertion of inner membrane proteins, particularly those of the carrier family. Although the new protein seemed to participate in mitochondrial import, it was not part of the well-characterized Tim17/Tim23 complex. Rather, Tim22 was recovered from detergent-solubilized mitochondria in a separate high molecular weight complex [42]. A second component, Tim54, was identified through a two hybrid interaction with the mitochondrial outer membrane protein Mmm1 [39]. Subsequent analysis revealed that Tim54 is an integral inner membrane protein and partners with Tim22. Inactivation of Tim54 in a temperature-sensitive *tim54* mutant inhibited import of AAC into isolated mitochondria [39].

Tim18 was recently identified because it interacted genetically with a temperature-sensitive *tim54* mutant [43] and co-immunoprecipitated with Tim54 [44]. Tim18 is an integral inner membrane protein that is 40% identical to Sdh4, the membrane anchor of succinate dehydrogenase [45]. Tim18, Tim22 and Tim54 with the tiny Tim proteins of the intermembrane space form a 300 kDa complex. While a direct role in protein import has not been established, Tim18 may regulate assembly of the 300 kDa complex because depletion of Tim18 yielded a functional complex of 250 kDa [43,44].

3.2. 'Tiny Tims' of the intermembrane space

A family of small proteins in the mitochondrial intermembrane space mediates import of inner membrane proteins across the intermembrane space [36–38,40,41]. Five proteins, Tim8, Tim9, Tim10, Tim12 and Tim13, have been identified in the yeast intermembrane space, while similar complements are present in other metazoans (Fig. 3). The amino acid sequences of the small Tim proteins are 25% identical and 50% similar to each other. They also share a 'twin CX_3C' motif, in which two cysteine residues are separated by three amino acids and each cysteine block is separated from the other by 11–16 amino acids [38]. This motif is reminiscent of a canonical zinc finger, but with a longer spacer [46]. Recombinant Tim10 and Tim12 fusion proteins bind zinc, and interaction between Tim10 and AAC is inhibited by zinc chelators [40], suggesting that the small Tim proteins bind zinc and that zinc binding is required for their function in vivo.

Tim10 and Tim12 were the first two identified components of the intermembrane space to mediate protein import [36,40]. Fractionation of yeast mitochondria showed that most of Tim10 was located in the soluble intermembrane space whereas Tim12 was peripherally bound to the outer surface of the inner membrane. Both proteins could be cross-linked chemically to a partly imported AAC precursor, indicating that they interact directly with the imported protein. However, the different intramitochondrial locations of Tim10 and Tim12 reflect their different functions in the import pathway. Inactivation or depletion of Tim12 did not interfere with import of AAC into the intermembrane space, but prevented insertion of AAC into the inner membrane. In contrast, inactivation or depletion of Tim10 blocked import of AAC, P_iC and Tim22 across the outer membrane. Thus, Tim10 functions before Tim12, probably by binding the incoming precursor as it emerges from the TOM complex.

Tim9 was identified as a partner protein with Tim10 through genetic and biochemical approaches [37,41]. Most of Tim9 is located in the mitochondrial intermembrane space as a soluble 70 kDa complex containing approximately equimolar amounts of the Tim9 and Tim10 [37,41]; the rest is present in the 300 kDa insertion complex. A single serine $\rightarrow$cysteine mutation in Tim9 allowed the protein to suppress the temperature-sensitive mutation in Tim10 [37].

The other two yeast proteins related to Tim10 and Tim12, Tim8 and Tim13 [38,47], were found in the intermembrane space as a distinct 70 kDa complex that could be separated from the Tim9/Tim10 complex by ion exchange chromatography [38]. Deletion of Tim8 or Tim13, alone or in combination, had no notable effect on cell growth and did not significantly affect import of AAC or P_iC into isolated mitochondria. However, deletion of Tim8 in combination with a temperature-sensitive Tim10 mutation was lethal [38]. Studies with a broader spectrum of precursors in strains lacking Tim8 or Tim13 revealed that Tim8/Tim13 mediated import of Tim23 [48]. Thus the Tim8/Tim13 complex most likely works in parallel with the Tim9/Tim10 complex by mediating the import of a subset of integral inner membrane proteins.

The specific route taken by the substrate to reach the inner membrane is still uncertain. One possibility is that the small Tim complexes act as chaperone-like molecules to guide the precursor across the aqueous intermembrane space, yielding a soluble intermediate in which the precursor is bound to the 70 kDa complexes in the intermembrane space (Fig. 3). This model is supported by import studies with temperature-sensitive *tim10* and *tim12* mutants, and by the fact that an AAC translocation intermediate bound to Tim10 in intact mitochondria is protected from added protease [36,37]. It predicts a transient complex in which Tim9/Tim10 or Tim8/Tim13 are bound directly to the precursor. Equally plausible is a model in which the 70 kDa complexes form a link between the TOM and the TIM complexes. In this model, the precursor is not released into the intermembrane space, but binds to the small Tim proteins as it emerges from the TOM complex. Further transfer to the Tim22/Tim54 complex could then occur without release into the intermembrane space. This model is supported by the recent finding that an AAC translocation intermediate is partially degraded by added protease [49]. It predicts a transient complex in which the TOM complex as well as the small Tim proteins are bound to the precursor.

3.3. Defective protein import: a novel type of mitochondrial disease

Humans contain at least six homologs of the small Tim proteins found in the yeast mitochondrial intermembrane space. One of these homologs had already been termed deafness–dystonia peptide (DDP1) because its loss results in the severe X-linked Mohr–Tranebjaerg syndrome, characterized by deafness, dystonia, muscle weakness, dementia and blindness [50,51].

DDP1 is most similar to yeast Tim8 and, when expressed in monkey or yeast cells, is located in mitochondria [38]. Mohr–Tranebjaerg syndrome is thus almost certainly a new type of mitochondrial disease caused by a defective protein import system of mitochondria. Loss of DDP1 function probably lowers the mitochondrial abundance of some inner membrane proteins that are critical for the function, development or maintenance of the sensorineural and muscular systems in mammals. The findings in yeast suggest that DDP1 functions as a complex with related partner proteins, perhaps with

hTim13. As mutations in DDP1 partner proteins may also be deleterious, and as all potential partner proteins are autosomally encoded, non-X-linked diseases with symptoms resembling those of Mohr–Tranebjaerg syndrome may well have a related etiology. Further, the link between a mitochondrial import defect and a neurodegenerative disease may provide insights into the molecular basis of other more frequent neurological diseases such as Parkinsonism that have been correlated with mitochondrial dysfunction.

4. Mitochondrial protein export pathways

As with protein import pathways, recent studies in protein export pathways for mitochondrially coded proteins have revealed new membrane components. While the topology of mitochondrial export resembles that of bacterial secretion, the yeast genome does not encode detectable homologs of the bacterial Sec translocase [1]. However, at least two pathways have been identified for protein export from the matrix to the inner membrane (Fig. 1). Oxa1 is a nuclear-coded inner membrane protein that mediates export of N- and C-tails of the mitochondrially coded precursor cytochrome *c* oxidase subunit II (Cox2) and also plays a role in ATP synthase formation [52–54]. Oxa1 interacts directly with nascent mitochondrially synthesized polypeptides [54]. However, its precise role in membrane insertion is not clear because *oxa1* mutants can be suppressed by mutations in the nuclear gene coding the cytochrome c_1 subunit of the bc_1 complex [53]. This suppression suggests that the conserved Oxa1 function can be bypassed in the membrane insertion process. Interestingly, Oxa1p has a homolog in the chloroplast, termed ALB3 in *Arabidopsis thaliana*, which is an essential protein involved in chlorophyll biosynthetic pathways [55].

A second export component, Pnt1, has been identified in an elegant genetic screen to identify yeast mutants defective for the export of mitochondrially coded proteins [56]. Pnt1 is an integral inner membrane protein facing into the matrix that mediates export of the C-terminus of Cox2. However, its precise role in export has not been determined because deletion of *pnt1* in *S. cerevisiae* did not impair Cox2 processing. Deletion of the *PNT1* ortholog from *Kluyveromyces lactis*, KlPNT1, resulted in a non-respiratory phenotype, absence of cytochrome oxidase activity, and a defect in the assembly of KlCox2 that appears to be due to a block of C-tail export. Thus, it may be possible that Oxa1 and Pnt1 have overlapping functions in *S. cerevisiae*. *PNT1* was previously identified as a gene that caused resistance to the antimicrobial drug pentamidine [57]. Given the coordination that must be required to assemble the large respiratory complexes of the inner membrane, one might expect that additional components will be identified.

5. Concluding remarks

Biogenesis of the various import components itself is complicated, with individual subunits using different pathways [47]. Tim54 is imported via Tim9/Tim10 [48] and inserted into the inner membrane through the TIM23 machinery [47], whereas Tim22 is imported via the TIM22 complex [36,41,47]. Import of the small Tim proteins bypasses the Tim machinery altogether, requiring Tom5, but no membrane potential [47]. The complex interplay between the different machineries may ensure coordinated regulation of the assembly of the mitochondrial protein import systems.

The recent discoveries of new import components and new import pathways imply how little we know about mitochondrial biogenesis, particularly the inner membrane, but also suggest that the answers to these questions will reveal exciting insights into a complicated biological process. Because new protein import components are still being identified, we are only at the tip of the iceberg when it comes to understanding the mechanisms of protein import.

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